The modern therapeutic aspects and prognostic factors of pancreas pseudocyst formation

Ph.D. thesis

2023

Lajos Szakó MD

Institute for Translational Medicine

University of Pécs, Medical School -

Faculty of Pharmacy

Doctoral School of Pharmaceutical Sciences

Leader of the Doctoral School: Prof. Dr. Erika Pintér

Program leader: Prof. Dr. Péter Hegyi

Consultant: Dr. Áron Vincze

Co-consultant: Dr. Bálint Erőss

1. Publications

Publications, on which the Ph.D. topic is based on

1. **L. Szakó**, N. Gede, A. Váradi, B. Tinusz, N. Vörhendi, D. Mosztbacher, Á. Vincze, T. Takács, L. Czakó, F. Izbéki, L. Gajdán, V. Dunás-Varga, J. Hamvas, M. Papp, K. E. Fehér, M. Varga, A. Mickevicius, I. Török, K. Ocskay, M. F. Juhász, S. Váncsa, N. Faluhelyi, O. Farkas, A. Miseta, A. Vereczkei, A. Mikó, P. J. Hegyi, A. Szentesi, A. Párniczky, B. Erőss, and P. Hegyi, "Early occurrence of pseudocysts in acute pancreatitis - A multicenter international cohort analysis of 2275 cases," **PANCREATOLOGY**, vol. 21, no. 6, pp. 1161–1172, 2021.
   Q1, number of citations: 9

2. **L. Szakó**, P. Mátrai, P. Hegyi, D. Pécsi, Z. Gyöngyi, D. Csupor, J. Bajor, B. Erőss, A. Mikó, Z. Szakács, D. Dobszai, Á. Meczker, K. Márta, I. Rostás, and Á. Vincze, "Endoscopic and surgical drainage for pancreatic fluid collections are better than percutaneous drainage: Meta-analysis," **PANCREATOLOGY**, vol. 20, no. 1, pp. 132–141, 2020.
   Q1, number of citations: 1

Publications related to the Ph.D. topic

1. D. Dobszai, P. Mátrai, Z. Gyöngyi, D. Csupor, J. Bajor, B. Erőss, A. Mikó, **L. Szakó**, Á. Meczker, R. Hágendorn, K. Márta, A. Szentesi, and P. Hegyi, "Body-mass index correlates with severity and mortality in acute pancreatitis: A meta-analysis," **WORLD JOURNAL OF GASTROENTEROLOGY**, vol. 25, no. 6, pp. 729–743, 2019.
   Q1, number of citations: 36

2. L. Szapáry, B. Tinusz, N. Farkas, K. Márta, **L. Szakó**, Á. Meczker, R. Hágendorn, J. Bajor, Á. Vincze, Z. Gyöngyi, A. Mikó, D. Csupor, P. Hegyi, and B. Erőss, "Intralesional steroid is beneficial in benign refractory esophageal strictures: A meta-analysis," **WORLD JOURNAL OF GASTROENTEROLOGY**, vol. 24, no. 21, pp. 2311–2319, 2018.
   Q1, number of citations: 12

Publications not related to the Ph.D. topic

1. F. Dembrovszky, S. Váncsa, N. Farkas, B. Erőss, **L. Szakó**, B. Teutsch, S. Bunduc, R. Nagy, D. Dohos, S. Kiss, A. Párniczky, Z. Vinkó, Z. Péterfi, and P. Hegyi, "Immunoglobulin Response and Prognostic Factors in Repeated SARS-CoV-2 Positive Patients: A Systematic Review and Meta-Analysis," **VIRUSES**, vol. 13, no. 5, 2021. *Q1, number of citations: 1*

2. A Kanjo, Z. Molnar, N. Zádori, N. Gede, B. Erőss, **L. Szakó**, T. Kiss, Z. Márton, M. L. N. G. Malbrain, K. Szuldrzynski, J. Szrama, K. Kusza, K. Kogelmann, and P. Hegyi, "Dosing of Extracorporeal Cytokine Removal In Septic Shock (DECRISS) : protocol of a prospective, randomized, adaptive, multicentre clinical trial," **BMJ OPEN**, vol. 11, no. 8, 2021. *Q1*

3. **L. Szakó**, N. Farkas, S. Kiss, S. Váncsa, N. Zádori, N. Vörhendi, B. Erőss, P. Hegyi, and H. Alizadeh, "Convalescent plasma therapy for COVID-19 patients : a protocol of a prospective meta-analysis of randomized controlled trials," **TRIALS**, vol. 22, no. 1, 2021. *Q1, number of citations: 1*

4. S. Váncsa, F. Dembrovszky, N. Farkas, **L. Szakó**, B. Teutsch, S. Bunduc, R. Nagy, A. Párniczky, B. Erőss, Z. Péterfi, and P. Hegyi, "Repeated SARS-CoV-2 Positivity: Analysis of 123 Cases," **VIRUSES**, vol. 13, no. 3, 2021. *Q1, number of citations: 13*

5. Z. R. Dömötör, N. Vörhendi, L. Hanák, P. Hegyi, S. Kiss, E. Csiki, **L. Szakó**, A. Párniczky, and B. Erőss, "Oral Treatment With Bisphosphonates of Osteoporosis Does Not Increase the Risk of Severe Gastrointestinal Side Effects : A Meta-Analysis of Randomized Controlled Trials," **FRONTIERS IN ENDOCRINOLOGY**, vol. 11, 2020. *Q1, number of citations: 1*

6. B. Erőss, Z. Molnár, Z. Szakács, N. Zádori, **L. Szakó**, S. Váncsa, M. F. Juhász, K. Ocskay, N. Vörhendi, K. Márta, A. Szentesi, A. Párniczky, P. J. Hegyi, S. Kiss, M. Földi, F. Dembrovszky, A. Kanjo, P. Pázmány, A. Varró, Á. Csathó, Z. Helyes, Z. Péterfi, L. Czopf, I. Kiss, A. Zemplényi, D. Czapári, E. Hegyi, D. Dobszai, E. Miklós, A. Márta, D. Tóth, R. Farkas, N. Farkas, B. Birkás, E. Pintér, G. Pethő, B. Zsigmond, A. Sárközi, A. Nagy, and P.

Hegyi, “Personalised health education against health damage of COVID-19 epidemic in the elderly Hungarian population (PROACTIVE-19) : protocol of an adaptive randomized controlled clinical trial,” **TRIALS**, vol. 21, no. 1, 2020. *Q1, number of citations: 3*

7. M. Földi, K. Farkas, S. Kiss, N. Zádori, S. Váncsa, **L. Szakó**, F. Dembrovszky, M. Solymár, E. Bartalis, Z. Szakács, P. Hartmann, G. Pár, B. Erőss, Z. Molnár, P. Hegyi, and A. Szentesi, “Obesity is a Risk Factor for Developing Critical Condition in COVID-19 Patients : a Systematic Review and Meta-analysis,” **OBESITY REVIEWS**, vol. 21, no. 10, 2020. *Q1, number of citations: 138*

8. S. Váncsa, P. J. Hegyi, N. Zádori, **L. Szakó**, N. Vörhendi, K. Ocskay, M. Földi, F. Dembrovszky, R. Z. Dömötör, K. F. Jánosi, Z. Rakonczay, P. Hartmann, T. Horváth, B. Erőss, S. Kiss, Z. Szakács, D. Németh, P. Hegyi, G. Pár, L. Frim, Z. R. Dömötör, Z., M. Imrei, Z. Molnár, Z. Péterfi, H. Alizadeh, and L. Czopf, “Pre-existing liver diseases and on-admission liver-related laboratory tests in COVID-19: a prognostic accuracy meta-analysis with a systematic review,” **FRONTIERS IN MEDICINE**, vol. 7, 2020. *Q1, number of citations: 9*

9. N. Zádori, S. Váncsa, N. Farkas, P. Hegyi, **L. Szakó**, N. Vörhendi, L. Frim, Z. R. Dömötör, Z. Szakács, S. Kiss, M. Földi, F. Dembrovszky, M. Imrei, Z. Molnár, Z. Péterfi, H. Alizadeh, L. Czopf, and B. Erőss, “The negative impact of comorbidities on the disease course of COVID-19,” **INTENSIVE CARE MEDICINE**, vol. 46, no. 9, pp. 1784–1786, 2020. *Q1, number of citations: 25*

2. **Scientometrics (25.01.2023.)**

Based on the MTMT:

Independent citations: 277

All citations: 292

Hirsch index: 7

Based on Google Scholar

All citations: 480

Hirsch index: 8

Impact factor:

2018: 3,411

2019: 3,665

2020: 23,855

2021: 30,133

2022: 30,297

3. Introduction

3.1. Etiology

Acute pancreatitis is an often-occurring gastrointestinal disease, which requires in-hospital care. Annual incidence of acute and chronic (CP) pancreatitis varies by country (13-100/100,000 persons)

In the case of AP, the presence of **gallstones** is between 40-70%, while only 3-7% of gallstone patients develop pancreatitis. Several factors play a role in the pathomechanism of gallstones causing AP, the most important of which is obstruction caused by gallstones around the papilla of Vater, and secondary obstruction due to edema formation.

25-35% of AP in the United States is caused by **alcohol consumption**. The mechanism of alcohol's direct damaging effect on the gland is not completely clear, but cell damage due to the high concentration of the alcohol dehydrogenase enzyme plays a role in its pathomechanism. In addition, ethanol stimulates enzyme secretion while increasing the tone of the sphincter of Oddi, raising the pressure within the duct of Wirsung, which also leads to the activation of enzymes within the organ through acinar cell damage.

The association of AP with the existence of **smoking** is a well-known fact, to which alcohol consumption can also contribute.

In 1-14% of cases, **hypertriglyceridemia** is the causative factor, and the causal role of both primary and secondary lipoprotein metabolism disorders is significant, among the latter obesity, hypothyroidism, and diabetes mellitus should be highlighted

Inflammation following **endoscopic retrograde cholangiopancreatography (post-ERCP)** occurs between 3-10%, and its patient-dependent and intervention-dependent risk factors are well known.

In the inflammation that develops based on **genetic susceptibility**, the CFTR gene, which also plays a role in cystic fibrosis, should be highlighted, as well as SPINK1 and CTRC gene mutations.

Drug-induced AP occurs rarely compared to other pathological factors and is characterized by a good outcome and low mortality. It often occurs during mercaptopurine, aminosalicylates, sulfonamides, didanosine, pentamidine, tetracyclines, azathioprine, estrogen, furosemide, hydrochlorothiazide, and steroid therapy.

Rare etiological factors also include traumatic origin, hypercalcemia, infections caused by pathogens, vascular diseases, and inflammation of unknown origin in the case of an undetectable pathological factor.

3.2. Diagnostics

The diagnosis of AP is based on the **revised Atlanta classification of 2012**, according to which at least two of the following three criteria must be present: 1.) upper abdominal pain, which is classically belt-like, radiating to the back, 2.) an increase in amylase and lipase levels at least three times the upper normal relative to the limit value, 3.) the presence of typical morphological changes of AP on imaging studies, which can be an ultrasound (US), computed tomography (CT), magnetic resonance (MR), endoscopic ultrasound (EUH) or magnetic resonance cholangiopancreatography (MRCP)

3.3. Severity

Based on the already mentioned Atlanta classification, the severity of AP can be divided into (1) mild, in which case there is no organ damage, (2) moderate, when there is only transient (<48 hours) organ damage and/or local complications are present, (3) finally severe category, in which case there is organ damage lasting more than 48 hours.

The BISAP point system can also be used to quickly determine the severity and prognosis, as well as the risk of death, in which case 1 point is awarded for each of the following existing criteria: (1) blood urea nitrogen level above 8.92 mmol/l (25 mg/dl), (2) altered mental status, for which the Glasgow Coma Scale (GCS) is the most widely accepted tool, (3) presence of systemic inflammatory response (SIRS), (4) age over 60 years, (5) presence of chest effusion. For a patient with a BISAP score of 0, the risk of mortality is less than 1%, while BISAP 5 can reach 22% mortality.

3.4. Treatment

AP always requires hospitalization, although its severity can vary. The main pillars of the treatment are fluid therapy, pain relief, and nutrition.

In terms of **fluid therapy**, we provide 5-10 ml/kg/hour of fluids using an isotonic crystalloid solution (e.g., physiological saline or Ringer's lactate solution) for all patients with AP, unless they have cardiovascular, renal, or other associated accompanying factors contraindicating aggressive fluid replacement.

Significant abdominal pain is the most common symptom of inflammation of the pancreas, which can also contribute to the development of hemodynamic instability, which is why the **administration of painkillers** is an important element of successful therapy. Fluid therapy, already discussed above, can also contribute to pain relief by alleviating ischemic pain caused by hemoconcentration and avoiding lactic acidosis. To relieve spasmodic abdominal pain, drugs with the active ingredient metamizole can be used as first-line pain-relieving therapy in combination with antispasmodics. In addition, opioids are safe and effective for pain relief in patients with acute AP.

Due to the potentially rapid course and severity of the disease, close **monitoring** of patients is necessary for the first 24-48 hours. If other organ complications develop, the duration of monitoring should be increased.

An integral part of the therapy is feeding the patient, which can be done orally, enterally, and parenterally. Oral feeding in AP can be restarted if the abdominal pain subsides and the inflammatory laboratory values decrease, which does not necessarily mean that the values str normalized, but only mean a decreasing trend. In case of inflammation of any origin, enteral feeding provides the best results, which can be done through a nasogastric or nasojejunal tube. Both elementary and polymeric formulas can be used.

After the occurrence of AP, it is important to **treat the underlying etiological factors** (e.g.: gallbladder removal following inflammation caused by gallstones) to prevent the development of further inflammation.

3.5. Fluid collections

Complications of AP can be divided into local and systemic complications. Local complications include acute edematous fluid collection (acute pancreatic fluid collection = APFC), acute necrotic fluid collection (ANFC), pseudocyst (PC), and walled-off necrosis (WON).

APFC usually develops within four weeks after inflammation in the case of edematous, non-necrotic inflammation and does not have the characteristics of PC, i.e. it does not have a defined wall and is usually located outside of the pancreas.

PC refers to a more advanced state of the fluid collection, which is usually located outside of the pancreas, does not contain necrosis, and has a well-defined wall. It usually appears weeks after the inflammation.

ANFC develops in the case of necrotizing AP and covers an entity without a wall, which can affect the organ and the tissues around the organ. It may contain both liquid and solid necrotic tissue debris.

WON is a more mature state of necrotic fluid collection, in which case the necrosis is surrounded by a wall, can be internal or external to the organ, and may still contain solid or liquid necrotic elements.

Among the listed fluid collections, **PC** is of outstanding importance due to its frequency. The circumscribed fluid with a wall that does not contain epithelium is surrounded by fibrous tissue. The occurrence of PC develops parallel to the occurrence of AP, although it occurs significantly less often in AP than in CP, and it occurs to a greater extent in alcohol-induced inflammation, which is also supported by the fact that it is the cause of PC in 59-78% of all cases. Regardless of etiology, the incidence of PC is 0.5-1/100,000 adults per year. There can be several ways of the formation of the entity in AP, but most often it is caused by damage to the pancreatic duct, which is followed by the outflow of pancreatic juice. In two-thirds of the patients, the connection between the cyst and the pancreatic duct can be proven, in the remaining one-third, probably due to inflammation, the connection cannot be proven. According to the Atlanta classification, PC usually develops after four weeks and has a defined fibrotic wall without epithelium. In CP, the method of cyst formation is less well known, two mechanisms may play a role: (1) during an acute flare-up, the already mentioned mechanisms cause damage to the duct and extravasation of pancreatic digestive enzymes, or (2) obstruction of the duct by protein plug, fibrosis, or stone fluid leakage occurs as a result of its blockage.

The **clinical presentation of PC** can be diverse, ranging from completely asymptomatic to the picture of an acute abdomen. Acute complications caused by the cyst, such as bleeding (which usually originates from a pseudoaneurysm of the splenic artery), infection, and rupture further alter the picture. Chronic complications include gastric obstruction, biliary obstruction, and splenic or portal vein thrombosis. After the imaging examination has confirmed the presence of a cystic lesion, the separation of PC from other cystic lesions of the organ, primarily from malignant tumors, requires special attention and is a differential diagnostic challenge. It is rare for patients to be admitted with jaundice or sepsis for PC. The presence of peritoneal signs of excitement indicates cyst rupture or infection. Other possible physical symptoms include fever, subicterus, or the presence of chest fluid (75).

Based on the literature, several **prognostic factors** have been identified that can predict the development of PC. Patients with fluid accumulation are typically significantly younger, alcoholic etiology is more common. It is accompanied by higher 48-hour CRP and LDH levels.

Imaging techniques prove to be diagnostically superior to laboratory tests. On the **transabdominal US**, PC appears as a hypoechoic structure, the well-defined (hyperreflective) fibrotic wall can be distinguished, which gives the lesion a spherical or oval shape. Due to the greater sensitivity of the **CT examination**, and due to the potentially present intestinal obstruction and flatulence in the acute phase, it is preferable to the US. **MRI imaging** is also a sensitive diagnostic method for the detection of PC, however, since CT is more accessible and meets all diagnostic needs, it is rarely used. **Endoscopic examination** is not mandatory in the diagnosis of PC, however, in certain cases, if local expertise and the location of the cyst allow, it can also represent definitive therapy. Both PC and WON should be **treated** if the disease causes symptoms for the patient (which in most cases is abdominal pain) or there is a strong suspicion of infection of the fluid collection.

Given that PC can disappear without intervention, **supportive care** may also be sufficient. This treatment includes fluid replacement, pain relief, and the administration of antiemetics. For patients who tolerate oral feeding, a low-fat diet can be used. If oral feeding is not possible because the patient does not tolerate it, based on what is described in the treatment of AP, the patient can be fed enterally if possible, or parenterally as a last resort.

If an intervention is performed, the appearance of minimally invasive techniques (percutaneous drainage (PD), endoscopic drainage (ED), minimally invasive surgery) ensures a wide range of treatment options, as well as conservative surgical drainage (SD), can also be used. The use of **PD** requires an experienced radiologist, as it is a CT- or US-guided intervention. During this treatment, a catheter is inserted percutaneously into the cavity of the fluid collection, through which the fluid can be drained. The US is excellent at visualizing the region required for intervention, so its use is preferred. After the fluid has been drained, the catheter can be removed, and the cyst cavity can be visualized with contrast material, which can be applied for follow-up. Although PD can be used very well and its success in certain cases is indisputable, its complication rate is higher compared to other interventions, and residual fistulas and infections occur several times. For this reason, appropriate expertise is required for the execution, and the cyst must be in the correct position. **SD** should usually be used as a last resort in patients in whom percutaneous and endoscopic drainage was unsuccessful or not feasible. As in all branches of surgery, the rise of minimally invasive techniques over open surgery is

observed, although few comparative studies are available. A drain is also implanted during **ED**, either on the wall of the stomach or duodenum (transmural drainage) or through the papilla (transpapillary drainage), while their combination may also occur. Transpapillary drainage is possible only if the PC communicates with the pancreatic duct, which occurs in half of the cysts.

In some cases, the decision between modalities is obvious, due to the localization of the fluid collection, or the expertise available or lack thereof in the given center; while in other cases similar results are expected from different modalities. The European Society of Gastrointestinal Endoscopy (ESGE) and the American Society of Gastrointestinal Endoscopy (ASGE) recommends the primary use of percutaneous or endoscopic drainage for infected fluid collections, based on the criteria listed above.

3. 4. Ph.D. thesis motivation, objectives

Due to the large number of PCs occurring in both AP and CP cases, as well as the importance of PC mentioned above (complications, high mortality, factors impairing the quality of life), the treatment of the entity and the mapping of its prognostic factors are of paramount importance. Our goal was to detect predisposing factors for PC in a multicenter, cohort study based on data taken from an international registry. We also aimed to compare the above-mentioned modalities used in the treatment, for which we used meta-analytical tools.

5. Studies

5.1. Risk factors and prognostic value of pancreatic PC

5.1.1. Methodology

Data source and patient characteristics

For our cohort study, we collected data from the multicenter international acute pancreatitis (AP) registry managed by the Hungarian Pancreatic Study Group (HPSG). All patients were diagnosed with AP based on the 2012 modified Atlanta classification, as well as the assessment of severity (31). A total of 2,275 AP cases contained valuable information on pancreatic morphology. Patients whose most recent imaging study did not show PC formation were classified as "no PC" (NO-P). Patients with a PC-positive imaging test during the first four days of hospital stay were classified into the "old pseudocyst" (OLD-P) group. In contrast, patients in whom PC was diagnosed on the fifth day or later were classified as "new pseudocysts" (NEW-P).

Using prospectively collected data, PCs were identified with the help of a trained radiologist colleague based on 2012 revised Atlanta classification.

The accuracy and quality of the collected data were ensured by a four-level quality control system. The essence of the methodology is provided by four separate persons who independently review the authenticity of the collected data. These individuals include two medical colleagues and two health administrator colleagues.

The statistical analysis was performed using the following statistical tests: in the case of discrete and non-normally distributed continuous variables, the Kruskal-Wallis test with a significance level of 0.05 was performed, followed by Dunn's posthoc test with the Holm-Šídák p-value correction, in which case the p-value the significance level was 0.025. In the case of categorical variables, we determined the frequency of occurrence of each group. In these cases, the Chi-square test was used to analyze the relationships between variables, or if the Chi-square test could not be performed, Fisher's exact test was performed. A p-value of less than 0.05 ($\leq$0.05) was defined as statistically significant. All analyzes were performed using R studio 1.3.1073, and Dunn's tests were performed using the Dunn. test package with the consultation and assistance of a biostatistician colleague.

The study was approved by the Scientific and Research Ethics Committee of the Health Science Council (TUKEB) (22254-1/2012/EKU). All participants gave written, informed consent to participate in the study.

5.1.2. Results

Association of male gender and alcoholic etiology with the OLD-P group

Patients in the OLD-P group were predominantly male compared to the NO-P group (72.2% vs. 56.1%, p = 0.0014).

63% of NEW-P can be diagnosed in the first two weeks.

In our cohort, the median time for the first detection of newly developed pseudocysts (NEW-P) was on day 9 (IQR1-3: 7-15) of the hospital stay, while it was 11 days (IQR 1-3: 7-16) from the onset of abdominal pain (Figure 1).

Both NEW-P and OLD-P worsen the course of the disease and are associated with longer hospitalization.

In the case of OLD-P, there were significantly more cases of moderate AP than in the case of NO-P (56.5% vs 19.33%; p <0.001). A significantly higher proportion of patients developed moderate and severe AP compared to the NO-P group (p <0.001). Patients stayed in the hospital significantly longer in both OLD-P (median: 10 days, IQR 1-3: 6.8-16.2, p <0.001) and NEW-P (median: 14 days, IQR 1-3: 8- 22, p <0.001) compared to the NO-P group (median: 8 days, IQR 1-3: 5-11). We could not detect statistically significant differences in mortality between the groups, but overall mortality was 5.2% in the NEW-P group compared to 2.8% overall mortality in the NO-P group, suggesting that there is a correlation between total mortality and NEW-P (Figure 1).

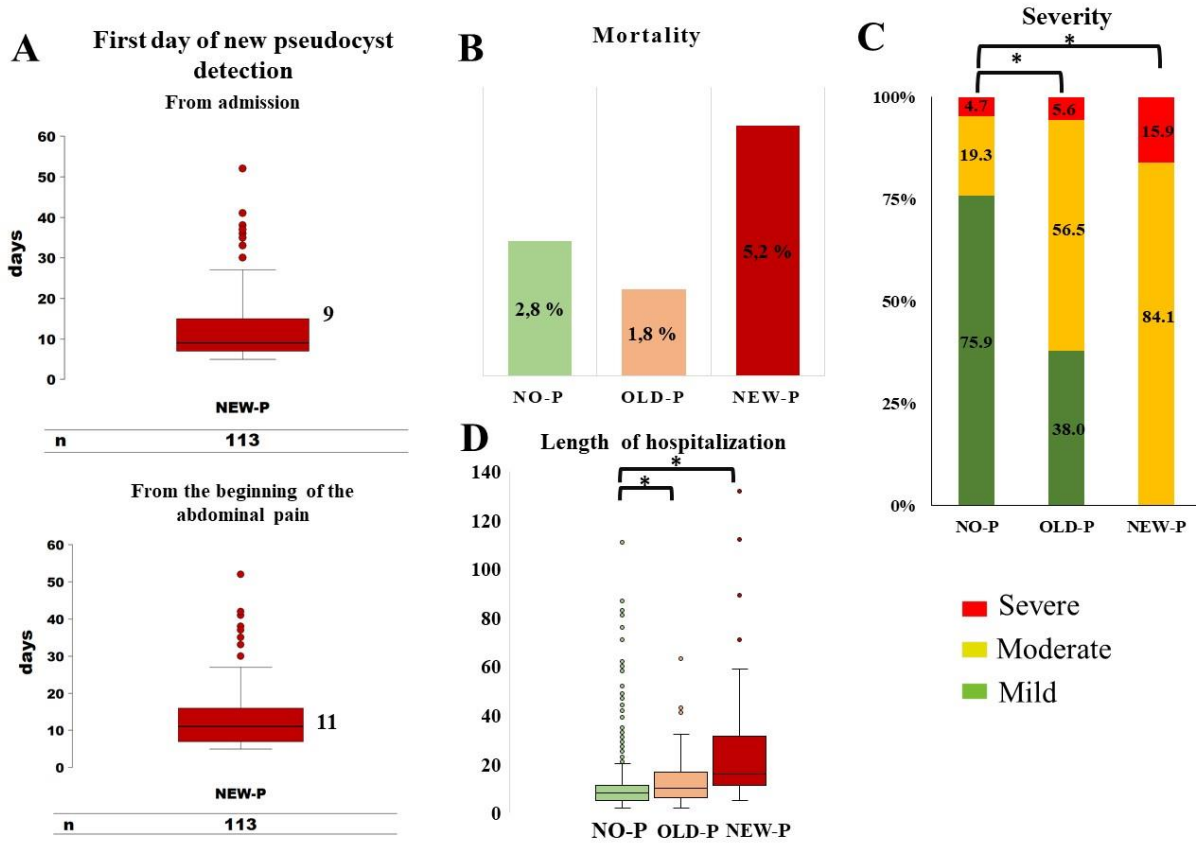

Figure 1: Outcomes A) Time of pseudocyst diagnosis from hospital admission and the onset of abdominal pain, B) total mortality, C) severity with percentage distribution within the group, D) length of hospital stay. Statistically significant differences were marked with *

Previous AP, CP, active smoking, and alcohol consumption are risk factors for OLD-P.

Previous AP episodes ($p < 0.001$), pre-existing diagnosis of CP ($p < 0.001$), active smoking ($p < 0.001$), and alcohol consumption (units/week) ($p = 0.014$) occurred significantly more in

OLD-P patients than in NO-P patients. On the other hand, previous smoking was associated with new-onset PC (p = 0.029). We could not detect significant differences in diabetes mellitus.

Abdominal defenses, vomiting and increased systolic and diastolic blood pressure present at admission are risk factors for NEW-P.

A significant difference was found in the comparison of NEW-P and NO-P in abdominal defense (25.7% vs 16.3%, p = 0.0155), diastolic blood pressure (88.38 ± 15.06 mmHg vs 84.14 ± 14.03 mm Hg, p = 0051), systolic blood pressure (150.89 ± 27.28 mm Hg vs. 140.70 ± 22.98 mm Hg, p = 0.0035) and vomiting (70% vs. 56.8%, p = 0.0088).

Lower admission amylase and lipase levels were typical for patients with OLD-P

Amylase and lipase levels on admission were significantly lower in the OLD-P group than in the NO-P group (770.6 ± 989.3 vs. 1094 ± 1129, p = 0.0003), however, this difference disappeared after excluding patients with recurrent AP or CP.

Lower body mass index (BMI) and laboratory parameters in OLD-P may indicate malnutrition

Regarding admission parameters, the BMI of patients in the OLD-P group was significantly lower (25.84 ± 6.63) compared to the NO-P group (28.09 ± 5.95, p <0.001) (Figure 5). Glucose (7.436 ± 2.433 vs. 8.338 ± 3.569, p = 0.0178) and cholesterol (4.593 ± 3.82 vs. 5.465 ± 4.02, p = 0.0081) levels were also significantly lower in OLD-P group compared to NO-P.

Decreased red blood cell parameters and increased platelet count are associated with the OLD-P group

The red blood cell count (4.417 ± 0.6212 vs. 4.699 ± 0.6231, p = 0.0002), hemoglobin (135.6 ± 09.90 vs. 142.9 ± 18.9, p = 0.0017), hematocrit (39.88 ± 5.363 vs. 41.65 ± 5.079, p = 0.0045) levels were lower, while platelet count (305 ± 128.7 vs. 249.6 ± 88.73 p = 0.0001) was higher in the OLD-P group compared to the NO-P group.

Increased white blood cell count, hemoglobin, hematocrit, glucose, blood urea nitrogen, LDH, and creatinine were associated with NEW-P

Patients admitted to the NEW-P group had a significantly higher white blood cell count (14.57 ± 4.411 vs. 12.89 ± 4.956, p = 0.0001), hemoglobin (150.1 ± 20.38 vs. 142.9 ± 18, 9, p = 0.0001), hematocrit (43.08 ± 5.445 vs. 41.65 ± 5.079, p = 0.0043), glucose (9.717 ± 3.633 vs. 8.338 ± 3.569, p < 0.001), urea nitrogen (7.07 ± 3.702 vs. 6.313 ± 3.837, p = 0.0125), lactate

dehydrogenase (592.2 ± 319.5 vs. 486.2 ± 315.5, p = 0.0002) and creatinine level (7.07 ± 3.702 vs. 6.313 ± 3.839, p <0.0125).

At admission, the calculated averages of LDH, GOT, GPT, total bilirubin, and gamma GT were lower, while the average CRP levels were higher in the OLD-P group.

Lactate dehydrogenase (420.6 ± 258.7 vs. 486.2 ± 315.5, p = 0.01), GOT (68.69 ± 117.7 vs. 156.2 ± 208.1, p <0.001), GPT (69.03 ± 141.2 vs. 154.7 ± 199.6, p <0.001), total bilirubin (27.83 ± 50.67 vs. 35.81 ± 39.28, p = 0.0005) and GGT (245.2 ± 372.2 vs. 362.9 ± 489.8, p <0.001) were lower in the OLD-P group, which can be attributed to the etiological differences. In addition, CRP (78.48 ± 82.94 vs. 49.97 ± 75.32, p <0.001) level was higher in the OLD-P group than in the NO-P group.

Systemic and local complications are more common in both OLD-P and NEW-P.

Regarding complications, acute pancreatic fluid collection (38.9% vs. 19% p <0.001), ascites (34.45 vs. 14.1 % p <0.001), systemic complication (13.15 vs. 7.8% p = 0.0113), respiratory failure (9.3% vs. 5.2% p = 0.0182) were more common in OLD-P compared to NO-P. CRP level reached a higher value during hospitalization (167 ± 104.3 vs. 147.8 ± 118.3, p = 0.0141) compared to the NO-P group. In addition, APFC (70.8 vs. 19% p <0.001), necrosis (38.1 vs. 7.8% p <0.001), and systemic complications (21.2 vs. 7.8 % p = 0.0245) were more common than in the NO-P group.

Every fourth patient with OLD-P, while every sixth patient with NEW-P required an intervention.

Interventions aimed at eliminating pancreatic PC were performed in 44 cases in our cohort. In the comparison of the two groups, there was no significant difference between the types of interventions; however, the rate of interventions was higher in the OLD-P group (23.1%) compared to the NEW-P group (16.8%).

5.1.3. Discussion

Among our results, one of the most important is that the majority of pancreatic PCs can be diagnosed even before the previously described four-week time point. 2012 revised Atlanta classification does not state that PC can be diagnosed only four weeks after AP; it only claims that their formation most often occurs after the mentioned time interval. Our analysis showed that at least half of PCs could be diagnosed in the first two weeks after inflammation based on the radiological morphological signs suggested by the Atlanta classification. For this reason,

we recommend the flexible use of the four-week time interval described in the classification for the diagnosis of pancreatic fluid collections. A possible earlier diagnosis may result in earlier treatment and a shortened hospital stay.

We observed an increased mortality rate in the OLD-P and NEW-P groups compared to the NO-P group, which might be a II. type of statistical error, that is, due to the low number of cases, we do not see a statistically significant effect of PC on mortality.

Based on our analysis, previous smoking and altered laboratory parameters may be included as risk factors for the development of a new PC.

Among the toxic effects that play a role in the formation of the cyst, alcohol and smoking should be highlighted, which also supports previous literature data. The association of PC with alcohol consumption is likely due to the direct toxic effects of alcohol on acinar and ductal cells. Both alcohol and smoking result in elevated intracellular calcium and adenosine triphosphate levels and mitochondrial permeability transition pore (MPTP) inhibition, leading to necrosis of both exocrine cell types. This can disrupt the integrity of the epithelial barrier, causing leakage of ductal fluid into the peri- or intra-pancreatic space.

Previous inflammatory episodes and chronic inflammation of the pancreas represent an increased risk for OLD-P, which is also consistent with the results of previous studies.

Based on previous reports, metabolic syndrome, including diabetes mellitus, high blood pressure, and obesity, have a detrimental effect on the course of pancreatitis (100). On the other hand, we found that patients with chronic pancreatitis (OLD-P group) had a lower BMI, indicating a greater degree of malnutrition in this group. In the OLD-P group, biliary AP occurred less often, which also appears in lower liver function tests, such as total bilirubin, glutamate oxaloacetate aminotransferase (GOT), glutamate pyruvate aminotransferase (GPT) and GGT (gamma-glutamyl transferase). . The exhaustion of the exocrine functions of the pancreas is indicated by significantly lower levels of amylase and lipase in the OLD-P group, as the number of acinar cells decreases in the case of chronic inflammation, which is also supported by the fact that the difference disappears when chronic pancreatic cases and recurrent AP are excluded from the analysis.

In addition to the above, the increased hemoglobin, hematocrit, blood urea nitrogen, and creatinine are probably due to dehydration at the time of admission. The significantly higher risk of systemic complications of NEW-P is partly caused by acute kidney damage, which is

reflected by significantly elevated blood urea nitrogen and creatinine levels. The diabetogenic status of the NEW-P group is shown by the increased level of admission glucose.

According to the recommendation of the European Society for Gastrointestinal Endoscopy (ESGE), interventions performed on pancreatic PCs should be performed when it causes symptoms or the fluid collection becomes infected. A detailed analysis of the treatment of fluid collections is discussed in detail in the meta-analysis described below. According to our analysis, less than a third of the patients required intervention. Nevertheless, this rate was higher in the OLD-P group, where endoscopic procedures were performed in more cases than percutaneous or surgical methods. Interestingly, percutaneous intervention was more common in the NEW-P group, the reason for which is presumably to be found in the localization of the PC. However, our analysis did not examine this issue.

5.2. Comparison of treatment modalities for PC and WON - a meta-analysis

5.2.1. Methodology

We used the acronym Population-Intervention-Control-Outcome [PICO] to state the clinical question of our meta-analysis. We included studies where patients with PC or WON (P) were treated surgically, percutaneously, or endoscopically (I and C) and compared at least two treatment modalities. Mortality, clinical success, recurrence, complications, and length of hospitalization (LOH) were compared as outcomes.

The meta-analysis was prepared following the Preferred Reporting Items for Systematic Review (PRISMA) guidelines and was registered in advance in the PROSPERO database (registration number: CRD42018079200).

Search strategy

A systematic search was performed in the electronic databases PubMed and Embase until December 2018 from baseline, using the following search key: ("pancreatic pseudocyst" OR "walled off necrosis") AND ("drainage" OR "surgery" OR" percutaneous" OR" endoscopy) ") AND (“drainage” OR “surgery” OR “percutaneous” OR “endoscopy”). The following filters were applied during the search: language: English, publication date: 1990 to December 2018.

Selection and exclusion criteria

Articles, that compared at least two intervention modalities about the outcomes described above and provided data on this comparison were included. We selected prospective and retrospective

controlled observational studies as well as randomized controlled studies. Conference abstracts with adequate data were also included. Non-English language studies, studies published before 1990, studies focusing on pediatric cases, case reports, and studies with combined interventions were excluded.

Selection process

The results were processed using EndNote X7.4 software (Clarivate Analytics, Philadelphia, PA, USA). Duplicates were removed with the help of the software. Two authors independently filtered the results first by title, then by abstract, and finally by full text according to pre-discussed criteria. If there was a contradiction between the two authors, a decision was made on the basis of consensus to include the study in question.

Data collection

The numerical data were collected in an Excel 2010 (Office 365, Microsoft, Redmond, WA, USA) workbook designed for this purpose. The investigators independently collected the relevant data from each publication: the number of subjects, data on the intervention, mortality, clinical success rate, recurrence, complications, post-intervention, total LOH, and treatment costs and then validated these data. Disagreements were resolved by consensus.

Statistical methods

Pairwise comparisons of ED, PD, and SD were performed for recurrence, complications, mortality, clinical success, and LOH. For binary and continuous results, odds ratios (OR) and weighted mean differences (WMD) were calculated with 95% confidence intervals (CI), using the random effect model (DerSimonian and Laird estimation), and the results were represented in a forest plot. Statistical heterogeneity was analyzed using the I2 statistic and the chi2-test, indicating the probability values. A p-value of less than 0.05 was considered significant when assessing both differences and heterogeneity. Where standard deviation and mean value were not reported for LOH, they were estimated from the median, interquartile range, and range using the method of Xiang Wan (2014).

Evaluation of the quality of studies

The quality assessment of the articles was performed by two authors independently, using the Newcastle-Ottawa scale for cohort and case-control studies, and the Jadad score for randomized controlled cases.

Subgroup analyses

Our further goal was to treat fluid collections not only as one entity, but also separately and to perform an analysis only in relation to WON and PC. We also compared endoscopic intervention with minimally invasive surgery, assuming that minimally invasive surgery provides better results than open surgery.

Assessment of the level of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system to evaluate the strength of our recommendations and the quality of our results.

5.2.2. Results

The result of the selection process

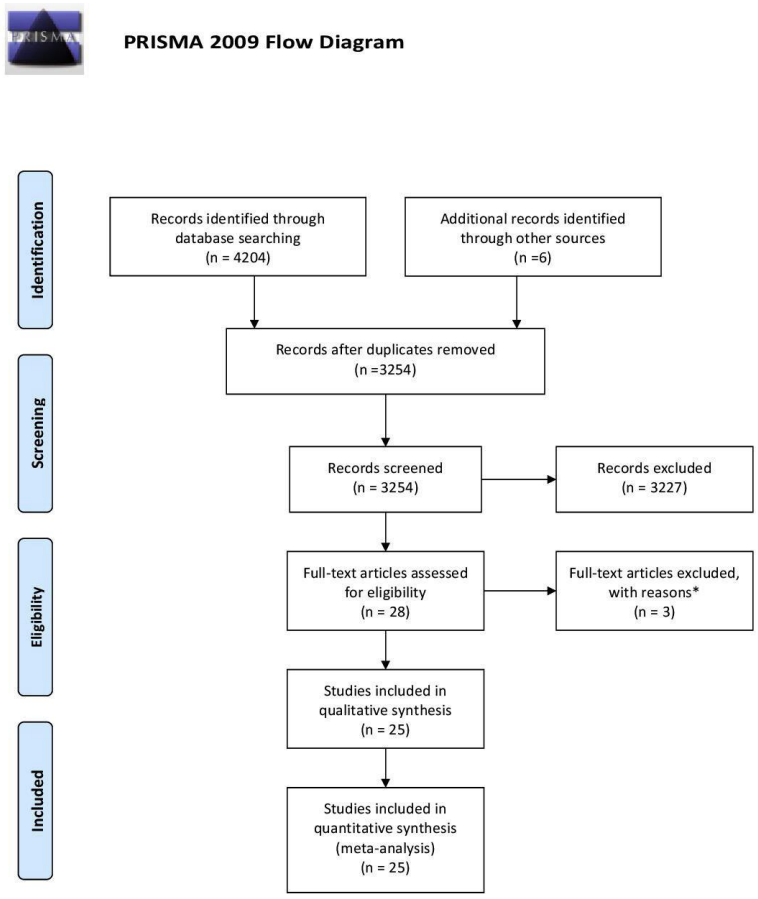

Figure 2: Selection results

We identified 1,341 and 2,863 articles in the Embase and PubMed databases, respectively. Finally, 24 relevant articles were included in the quantitative synthesis of this meta-analysis (Figure 2).

General and demographic characteristics of the studies

Among the 24 articles, five studies were only available as conference abstracts. Two prospective observational studies, two randomized controlled trials, and 20 retrospective observational studies were included in the quantitative synthesis.

Percutaneous versus endoscopic intervention

PC and WON together

Six studies compared ED and PD (including 688 and 286 patients, respectively). Of these, four compared PC/WON recurrence, three complications, two mortality, four clinical success, and two post-interventional LOH.

ED was found to be more successful (OR = 3.36; 95% CI 1.48, 7.63; p = 0.004, I2 = 68.9%, p = 0.022) than PD. Mortality (OR = 0.26; 95% CI 0.01, 4.55; p = 0.353, I2 = 58.5%, p = 0.0121), complications (OR = 1.36; 95% CI 0.52, 3.56; p = 0.531, I2 = 18.6%, p = 0.293), recurrence (OR = 0.37; 95% CI 0.10, 1.38; p = 0.138, I2 = 66 .4%, p = 0.03) and LOH (weighted mean difference (WMD) (day) = -30.58; 95% CI -74.87, 13.71; p = 0.009, I2 = 98 %, p <0.001) did not differ significantly between the two methods.

PC only

Five articles compared ED and PD in relation to PC (based on data from 579 and 231 patients, respectively). Of these, one article included data on mortality, three on recurrence, three on clinical success, two on complications, and one on LOH. The recurrence rate (OR = 0.23; 95% CI 0.08, 0.66; p = 0.006, I2 = 35.1%, p = 0.214) showed a significant difference favoring ED. Clinical success (OR = 2.84; 95% CI 0.90, 8.98; p = 0.076, I2 = 74.8%, p = 0.019) and complications (OR = 0.87; 95% CI 0.31, 2.43; p = 0.777, I2 = 0.0%, p = 0.737) did not differ significantly between the two interventional methods.

Surgical versus endoscopic intervention

PC and WON together

Fourteen articles compared ED with SD (842 and 896 patients, respectively). Of these articles, six reported on mortality, thirteen on clinical success, ten on recurrence, ten on complications, five on postoperative LOH, two on total LOH, and three on costs.

We found a significant difference in post-interventional LOH (WMD (day) = -4.61; 95% CI -7.89, -1.33; p = 0.006, I2 = 93.5%, p < 0.001) and in complete LOH (WMD (day) = - 3.67; 95% CI -5.00, -2.34; p < 0.001, I2 = 75.2%, p = 0.045), favoring endoscopic intervention.

Clinical success in ED was lower than SD (OR = 0.59; 95% CI 0.37, 0.93; p = 0.022, I2 = 19.2%, p = 0.250), but mortality (OR = 0.86, 95% CI 0.15, 5.06, p = 0.870, I2 = 0.0%, p = 0.378), recurrence (OR = 1.79, 95% CI 0.93, 3.35; p = 0.068, I2 = 27.2%, p = 0.211),

complication rate (OR = 0.75; 95% CI 0.45, 1.25; p = 0.264, I2 = 3.4%, p = 0.406), and cost (WMD (USD) = -3683.54; 95% CI -7723.38, -356.30; p = 0.074, I2 = 98.7%, p < 0.001) were similar between the two methods .

PC only

Eleven articles compared the endoscopic and surgical intervention of PCs (based on the data of 739 and 797 patients, respectively). Among them, mortality was compared in four studies, recurrence in eight, clinical success in ten, complications in seven, and LOH after the intervention in four. A significant difference can be established in clinical success (OR = 0.54; 95% CI) 0.35, 0.85; p = 0.007, I2 = 13.1%, p = 0.322) and recurrence (OR = 1.80; 95% CI 1.16, 2.79; p = 0.009, I2 = 0.0%, p = 0.456), both of which favored SD. Mortality (OR = 0.86; 95% CI 0.15, 5.06; p = 0.870, I2 = 0.0%, p = 0.378), complications (OR = 0.82; 95% CI 0, 44, 1.51; p = 0.523, I2 = 10.6%, p = 0.248) and LOH (WMD (day) = -5.07; 95% CI -11.26, -1.12; p = 0.109, I2 = 94.2%, p <0.001) was not significantly different.

Just WON

Four articles compared endoscopic intervention with surgery (based on the data of 100 and 99 patients respectively), including only WON in the analysis. Two of these articles compared mortality, two compared recurrence, three compared clinical success, and three compared complications. There was no significant difference between the two intervention methods in terms of mortality (neither death occurred), clinical success (OR = 1.01; 95% CI 0.23, 4.43; p = 0.990, I2 = 40.1 %, p = 0.188), recurrence (OR = 0.8; 95% CI 0.03, 18.72; p = 0.889, I2 = 75.0%, p = 0.046) and complications (OR = 0, 56; 95% CI 0.19, 1.71; p = 0.311, I2 = 14.6% for p = 0.310). A comparison of LOH and cost was not made due to to the small amount of data.

Minimally invasive SD vs ED

PC and WON together

Five articles compared endoscopic versus minimally invasive surgery (involved 172 and 103 patients, respectively). Two articles compared mortality, three recurrence, five clinical success, and four complications. There was no difference between minimally invasive SD and endoscopic intervention in terms of mortality (there were no deaths), clinical success (OR = 0.53; 95% CI 0.19, 1.49; p = 0.232, I2 = 37.3%, p = 0.172), recurrence (OR) = 2.7; 95% CI 0.44, 16.54; p = 0.281, I2 = 0.00%, p = 0.559) or complications (OR = 0.68; 95% CI 0.28, 1.16; p = 0.377, I2 = 0.00%, p = 0.831).

PC only

Based on three articles, we compared endoscopic treatment with minimally invasive surgery, which only included data on patients diagnosed with PC (110 and 44 patients, respectively). Of these, one article dealt with mortality, two with recurrence, three with clinical success, and two with complications.

There was no significant difference in mortality, clinical success (OR = 0.48; 95% CI 0.11, 2.13; p = 0.332, I2 = 53.8%, p = 0.115), recurrence (OR = 1 .29; 95% CI 0.06, 28.09; p = 0.873) and complications (OR = 0.47; 95% CI 0.14, 1.61; p = 0.230, I2 = 0.00%, p = 0.648) between the two treatment modalities.

Just WON

Two articles compared endoscopic intervention with minimally invasive surgery, including only patients diagnosed with WON (62 and 59 patients, respectively). Of these, one dealt with mortality, one with recurrence, two with clinical success, and two with complications. There was no significant difference in mortality (no deaths), recurrence (OR = 4.00; 95% CI 0.43, 37.46; p = 0.225), clinical success (OR = 0.6; 95% CI 0.08, 4.72; p = 0.625, I2 = 50.8%, p = 0.154) and complications (OR = 0.97; 95% CI 0.28, 3.31; p = 0.963, I2 = 0 .00%, p = 0.952).

Surgical versus percutaneous intervention

PC and WON together

Eleven articles compared the outcomes of PD and SD (involving 8530 and 7300 patients, respectively), of which seven reported data on mortality, six on clinical success, six on recurrence, five on complications, and two on LOH.

Recurrence rate (OR = 4.91; 95% CI 1.82, 13.22; p = 0.002, I2 = 66.5%, p = 0.011) and clinical success (OR = 0.13; 95% CI 0.07, 0.22, p <0.001, I2 = 0.0%, p = 0.774) was significantly better in SD compared to PD. Mortality (OR = 2.23; 95% CI 0.81, 6.15 p = 0.120, I2 = 31.2%, p = 0.213), complication rate (OR = 1.27 95% CI 0.28 , 5.82; p = 0.759, I2 = 79.8%, p = 0.001) and LOH (WMD (day) = 16.49 95% CI -4.09, 37.07; p = 0.074, I2 = 98.7, p <0.001) did not differ between the two modalities.

5.2.3. Discussion

In our analysis, percutaneous intervention produced worse results compared to endoscopic intervention. Clinical success was significantly higher in the ED group. Comparing only PCs,

there were significantly fewer recurrences after ED. However, insufficient data were available to compare the treatment of WON.

Surgery provides greater clinical success and a lower recurrence rate than PD. In the case of percutaneous intervention, the high complication rate was due to the developing and remaining fistulas.

Finally, shorter LOH favors endoscopic procedures compared to surgery. Although SD showed a higher success rate and a lower recurrence rate than ED, significant heterogeneity can be observed regarding both outcomes. The two methods appear to be equally effective for other outcomes. Considering only WON cases, we found no significant difference between surgery and endoscopy. We also found no significant difference when comparing minimally invasive surgery and endoscopic intervention. Our results are also supported by the existing literature.

Summarizing our results, as well as taking into account the current evidence for the treatment of pancreatic fluid collections, we recommend the following treatment protocol. During the treatment of symptomatic pancreatic fluid collections, it is necessary to choose the therapy based on the location of the collection. If multiple treatment modalities are discussed based on the localization of the fluid collection, it is recommended to start the treatment according to the principle of gradualness by choosing the least invasive intervention possible, in case of failure, the therapy can be escalated to more invasive procedures. Among the more minimally invasive interventions, the endoscopic intervention should be preferred over the percutaneous solution (Figure 3).

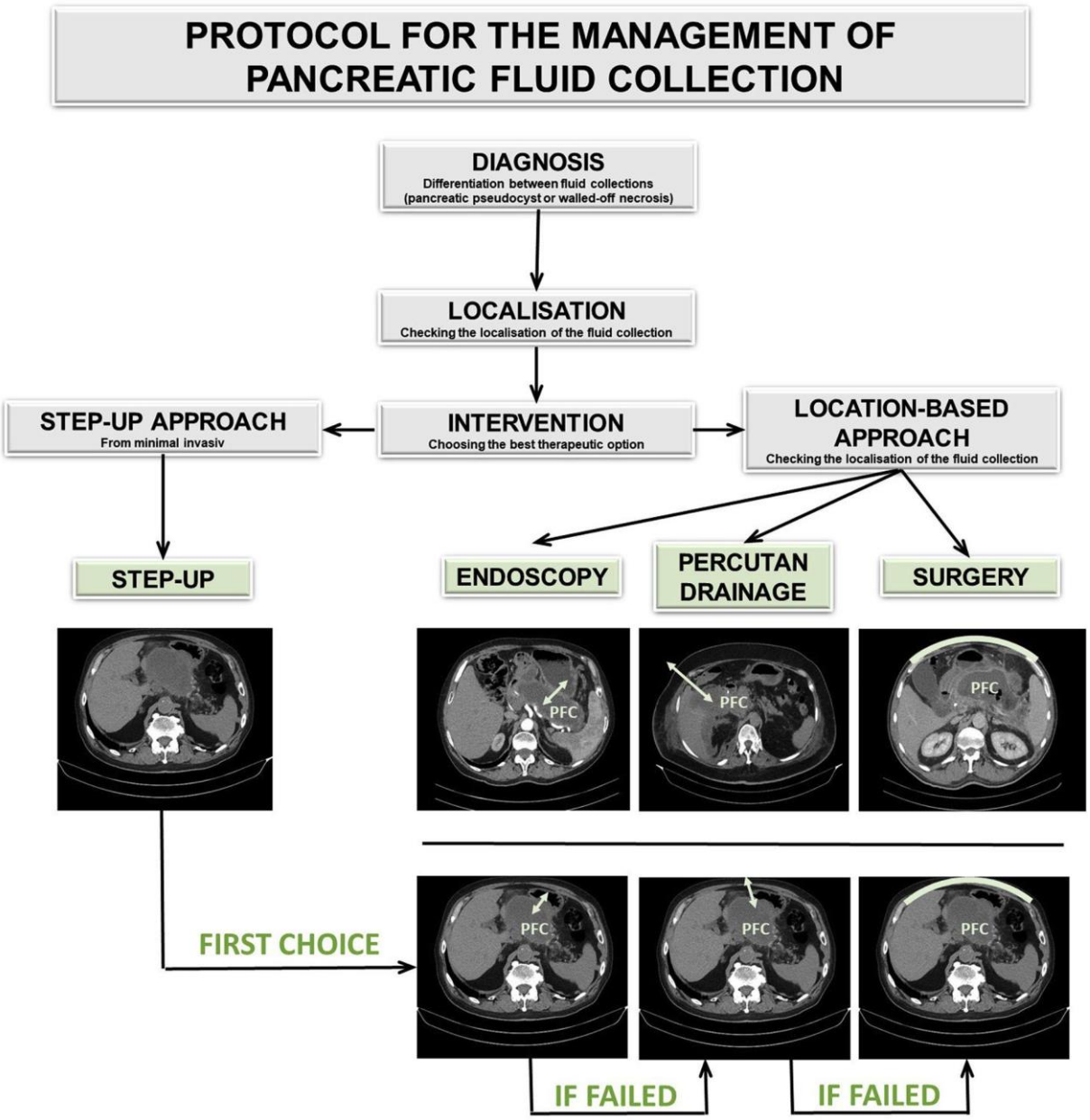

Figure 3: Recommended treatment protocol for pancreatic fluid collections.

Limitations

The overall quality of evidence (GRADE) was very low. Heterogeneity is very significant in some results. Our analysis included only two randomized clinical trials. In most studies, there were few patients, thus the total number of cases is also low. The difference between the number of patients comparing endoscopic and percutaneous drainage is very significant. Furthermore, we did not perform a subgroup analysis to compare different types of endoscopic intervention. The six conference abstracts that provided sufficient data for the analysis also carry the possibility of bias. The definition of clinical success was different between studies, which also causes great heterogeneity. The length of the follow-up period after the intervention also varied,

the shortest follow-up was 3 months (in 2 studies), the longest follow-up period was 38 months, while this was not determined in 11 studies. We included studies written in English only.

Conclusion

Treatment of inflammatory pancreatic fluid collections is strongly influenced by local expertise and radiological findings, such as the location and size of the collection. Surgery, percutaneous drainage, and endoscopic intervention are all accepted treatment methods, and each method has a specific patient group where it is more favorable than other types of intervention.

According to our meta-analysis, endoscopic intervention and surgery appear to be equally effective, although endoscopic methods provide shorter LOH. Percutaneous drainage is less favorable than the other two modalities. In order to eliminate the significant heterogeneity and provide a higher level of evidence, an objective, uniform definition of the outcomes (e.g.: clinical success) and further prospective randomized multicenter studies are needed.

6. Summary of results, conclusion, clinical applicability

PCs that develop as a result of acute inflammation of the pancreas have a prognostic role because in their case organ failure occurs more often, and they also show an association with severity, which can also lead to longer hospital stays and increased mortality.

PCs can be diagnosed earlier than we thought, more than half of the newly formed cysts can be found with imaging modalities in the first two weeks.

Regarding previously developed PCs, male gender and alcoholic etiology, previous AP episode, active smoking, lower amylase, lipase, hemoglobin, hematocrit, red blood cell, LDH, GOT, GPT, total bilirubin, gamma-GT level, and lower BMI at admission are also risk factors.

Abdominal protection at admission, vomiting, increased systolic and diastolic blood pressure, increased white blood cell count, hemoglobin, hematocrit, glucose, blood urea nitrogen, LDH, and creatinine are risk factors for newly developing cysts.

Every fourth patient with OLD-P, while every sixth patient with NEW-P required an intervention.

About what was described above, we recommend taking steps towards the diagnosis of fluid collections in the case of the mentioned pathological parameters, and when establishing the diagnosis, placing the morphological signs in the foreground, while not insisting on the previously used time interval.

If the fluid collection is to be intervened, local professional experience and the location of the fluid collection must be taken into account when deciding on the therapeutic modality. If several modalities are involved, it is worth choosing the endoscopic intervention, after its possible failure, applying percutaneous intervention, and then only finally performing open surgery.

7. Acknowledgment

I would like to express my gratitude to my supervisor and mentor **Dr. Bálint Erőss**, head of the Medical Group of the Translational Medicine Institute of the University of Pécs, for his daily guidance, help, and cooperation during my Ph.D. work. Also, the professional administration of **Dr. Áron Vincze**, associate professor of Internal Medicine Clinic No. 1 of the PTE Clinical Center, the provision of the clinical background necessary for my Ph.D. work, and proofreading of our publications. I would like to thank **Professor Dr. Péter Hegyi**, head of the PTE Institute of Translational Medicine, for the opportunity to participate in the Ph.D. program, as well as for the scientific and professional development, without his insights, it would not have taken place. Thanks also go to **Dr. Professor Kálmán Tóth** and **Dr. Péter Kanizsai** for providing the clinical background necessary for the realization of my work. I am indebted to **Dr. Andrea Szentesi**, head of the multidisciplinary group, **Emőke Miklós**, head of the clinical administrator group, **Richárd Farkas**, head of the IT group, **Dr. Nelli Farkas**, head of the statistics group, **Dr. Szabolcs Kiss**, coordinator of the meta-analysis working group, as well as **the Hungarian Pancreas Working Group** and to **all employees of the Institute of Translational Medicine**. Special thanks to **Dr. Noémi Zádori, Dr. Nóra Vörhendi, and Dr. Szilárd Váncsa** for their professional and friendly support.

I would also like to express my gratitude to my wife, parents, sisters, and friends for their trust and support, without which the birth of this work would not have been possible.